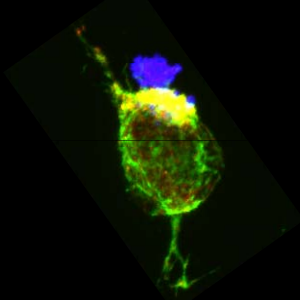
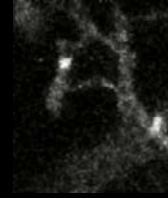


The regulation of myelin phagocytosis by the cytoskeleton

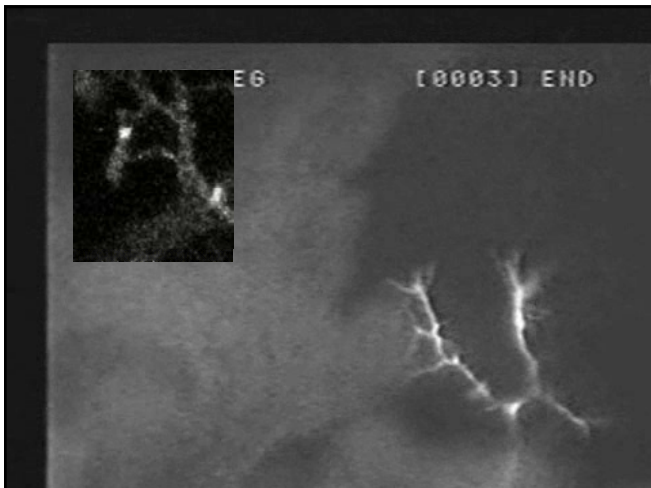


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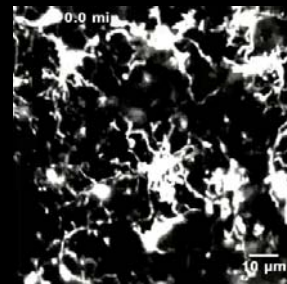
In-vivo imaging "resting" microglia GFP^+ by time lapse two-photon microscopy



Nimmerjahn, Kirchhoff & Fritjof, *Science*, 2005

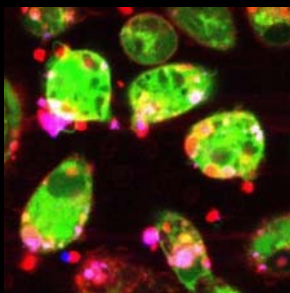


In-vivo imaging of injury activated microglia GFP^+ by time lapse two-photon microscopy



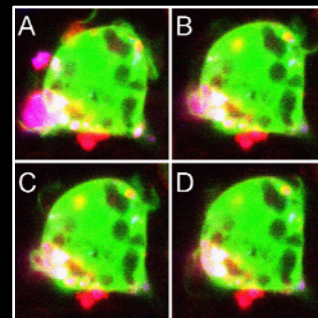
Davalos, Grutzendler, Yang, Kim, Zuo, Jung, Littman, Dustin & Gan, *Nature Neuroscience*, 2005

Phagocytosis of degenerated-myelin by time lapse confocal microscopy



Hadas, Reichert, Spira, Hanisch & Rotshenker, *J. Neuroinflammation*, 2012

Phagocytosis is a process whereby phagocytes "eat" large particles ($> 0.5\mu\text{M}$)



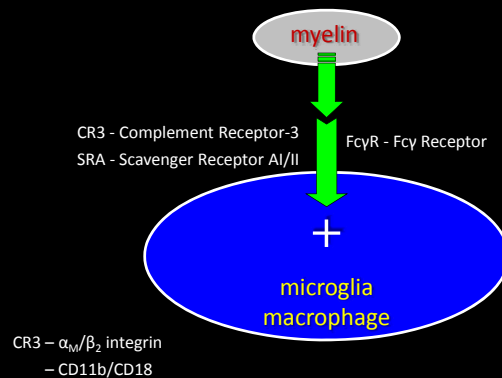
Hadas, Reichert, Spira, Hanisch & Rotshenker, *J. Neuroinflammation*, 2012

Degenerated-myelin is harmful

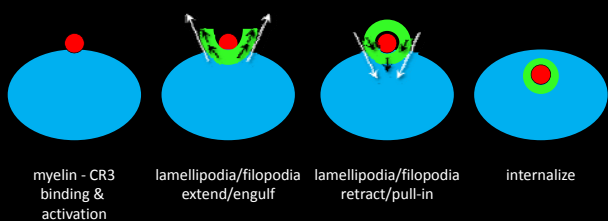
- Inhibits the regeneration of severed adult axons
- Inhibits remyelination by oligodendrocyte precursors
- Activates the complement system to produce membrane attack complexes which produce damage to nearby intact myelin and axons

The clearance of degenerated-myelin is critical for repair and for minimizing damage

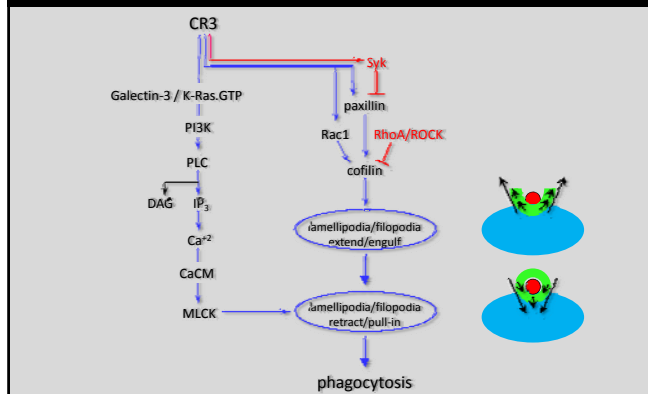
Phagocytic receptors mediate phagocytosis



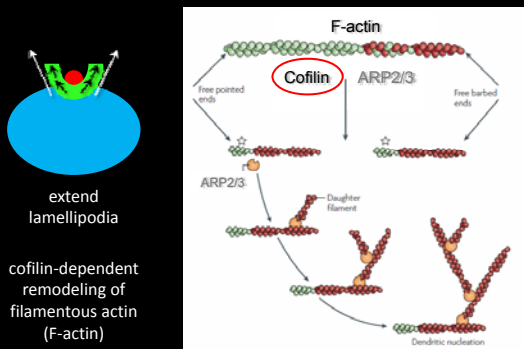
CR3-mediated myelin phagocytosis: engulfment and internalization



The signaling network of myelin phagocytosis

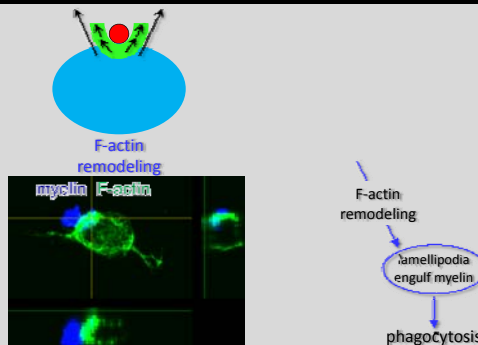


Cofilin-dependent remodeling of F-actin leads to the production of membrane protrusions



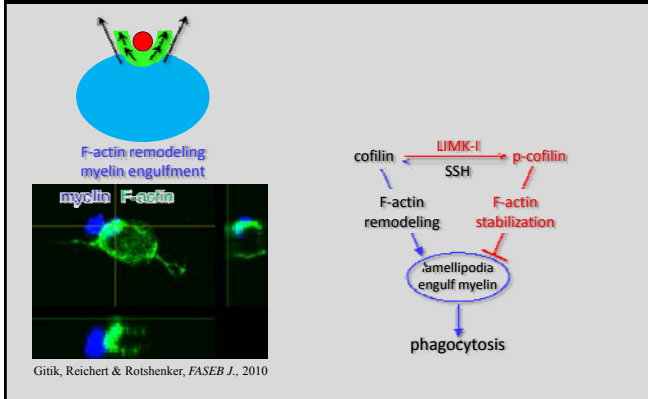
Wang, Eddy & Condeelis, *Nature Reviews Cancer*, 2007

Remodeling of F-actin occurs at the onset of myelin phagocytosis

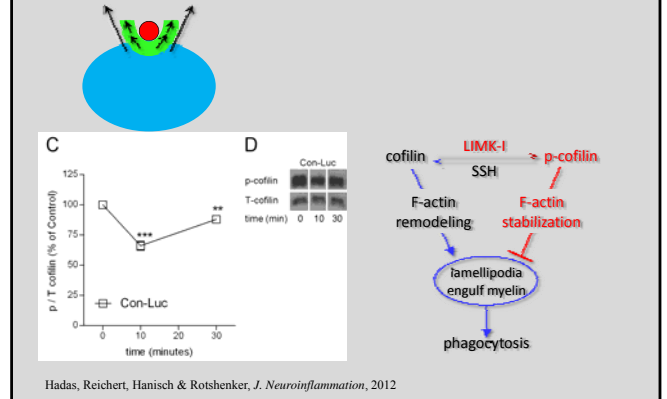


Gitik, Reichert & Rotshenker, *FASEB J.*, 2010

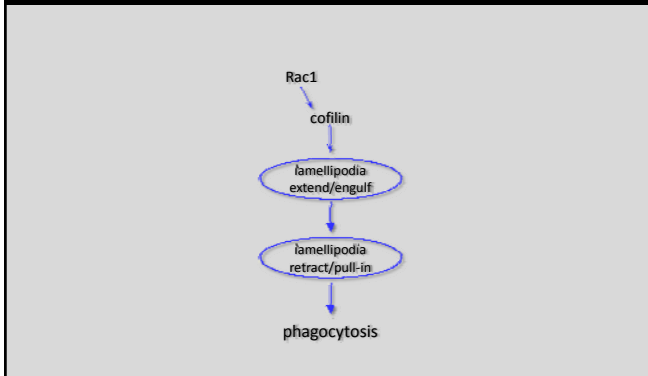
Cofilin-dependent engulfment of myelin



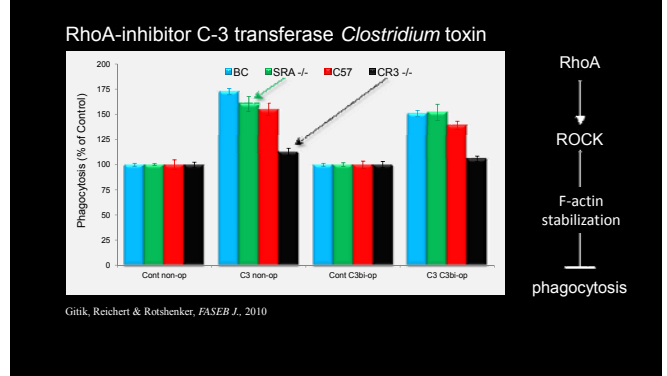
Cofilin is transiently activated during myelin phagocytosis



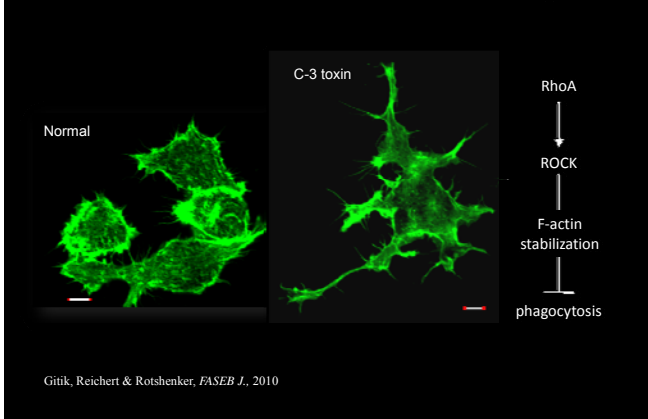
Does Rac1 activate myelin phagocytosis by advancing cofilin activation?



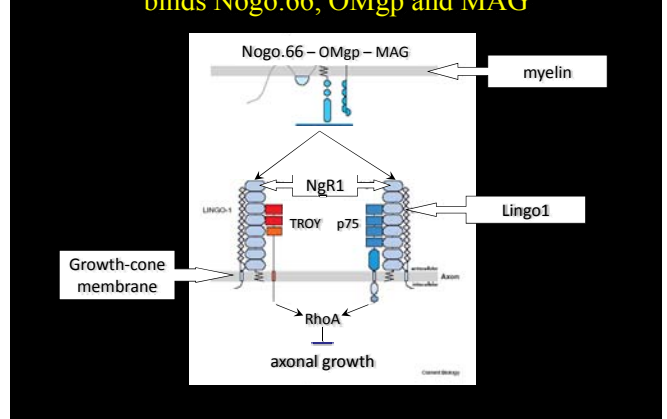
RhoA down-regulates CR3-mediated myelin phagocytosis



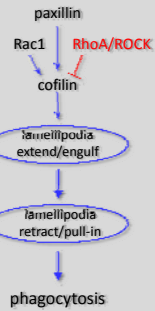
RhoA/ROCK stabilizes F-actin in microglia



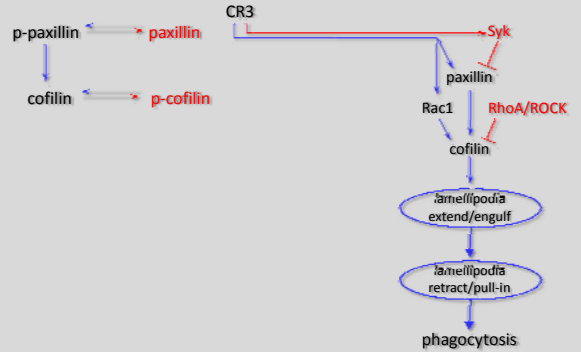
NgR1/Lingo1/(p75^{NTR} or TROY) receptor complex binds Nogo.66, OMgp and MAG



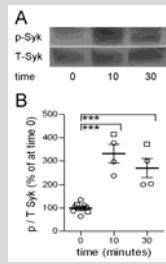
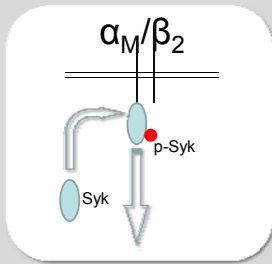
Does paxillin activates myelin phagocytosis by advancing cofilin activation?



Paxillin and cofilin activation correlate during myelin phagocytosis



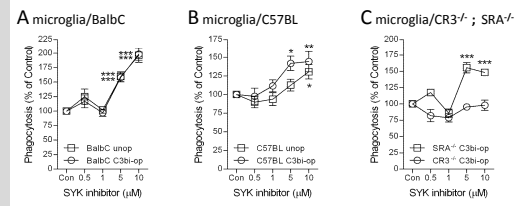
Syk is a non-receptor tyrosine kinase that CR3 recruits upon activation



Hadas, Reichert, Spira, Hanisch & Rotshenker, *J. Neuroinflammation*, 2012

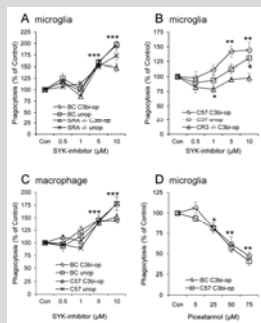
Syk negatively controls myelin phagocytosis by CR3 but not by SRA

SYK-inhibitor augmented phagocytosis by CR3 but not by SRA



Hadas, Reichert, Spira, Hanisch & Rotshenker, *J. Neuroinflammation*, 2012

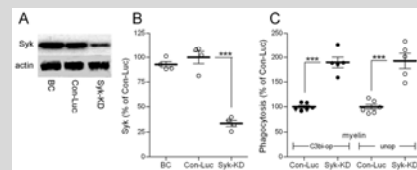
SYK-inhibitor augmented whereas piceatannol inhibited myelin phagocytosis



Hadas, Reichert, Spira, Hanisch & Rotshenker, *J. Neuroinflammation*, 2012

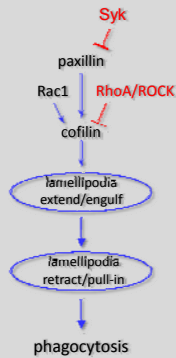
Syk negatively controls myelin phagocytosis

Syk-knockdown (Syk-KD) augmented myelin phagocytosis as did SYK-inhibitor



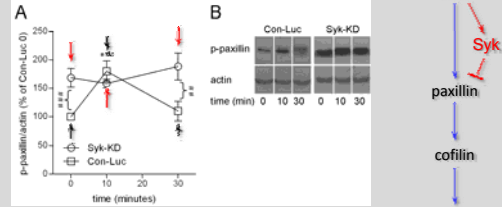
Hadas, Reichert, Spira, Hanisch & Rotshenker, *J. Neuroinflammation*, 2012

Does Syk down-regulate myelin phagocytosis through paxillin/cofilin?



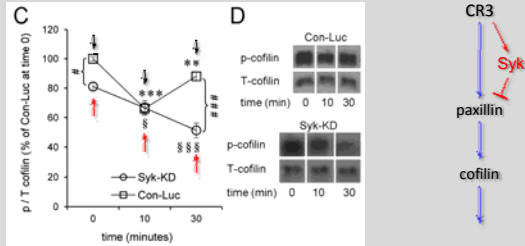
Syk advances paxillin inactivation

paxillin activation is continuously augmented in Syk-KD microglia



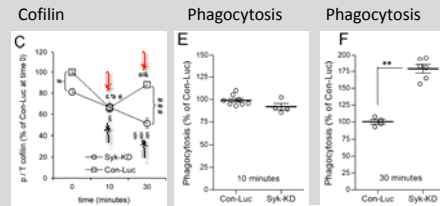
Syk advances cofilin inactivation

cofilin activation is progressively augmented in Syk-KD microglia



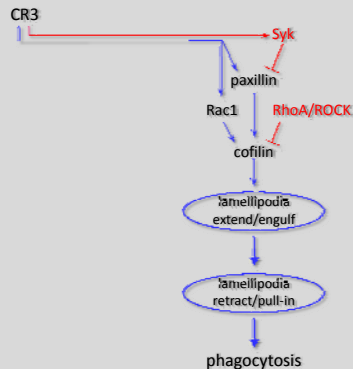
Hadas, Reichert, Hanisch & Rotshenker, *J. Neuroinflammation*, 2012

Syk advances cofilin inactivation, leading to the inhibition of myelin phagocytosis

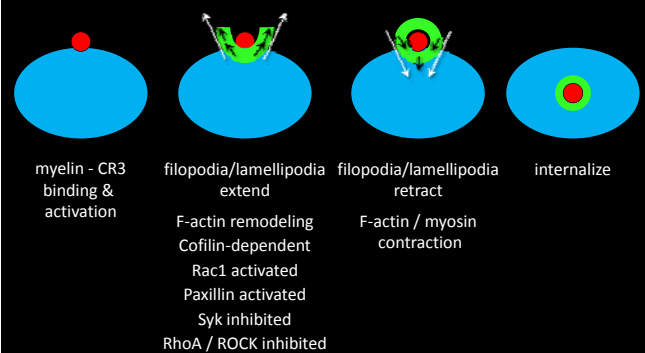


Hadas, Reichert, Hanisch & Rotshenker, *J. Neuroinflammation*, 2012

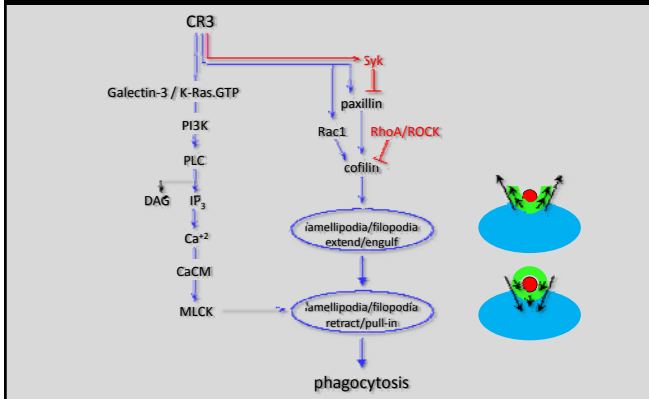
CR3 self-limits the phagocytosis of degenerated-myelin that CR3 itself carries out



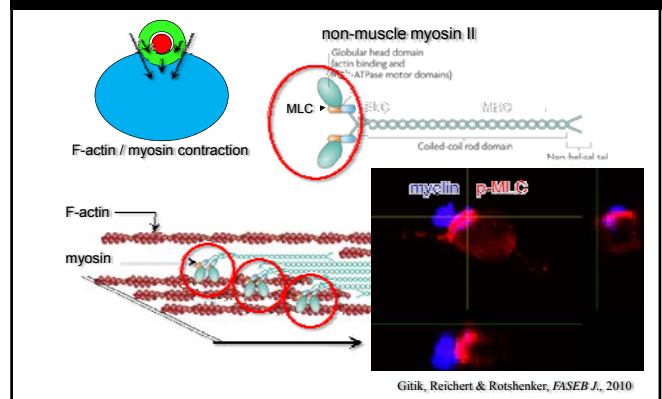
CR3-mediated myelin phagocytosis: engulfment and internalization



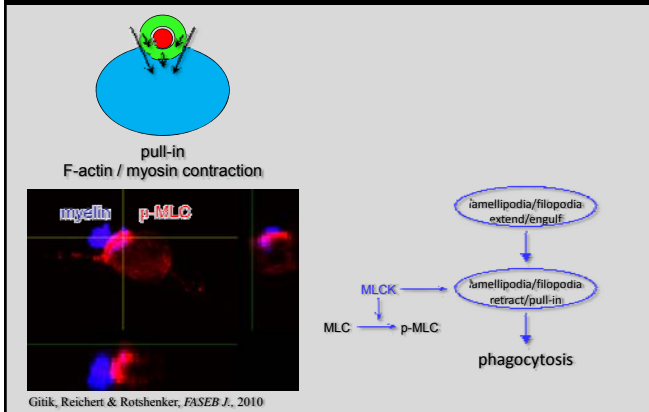
The signaling network of myelin phagocytosis



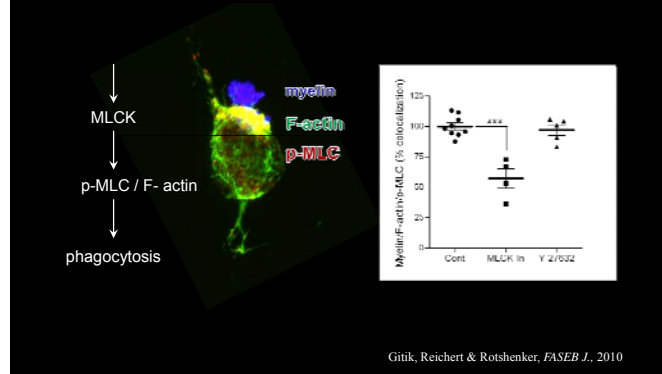
MLCK-dependent F-actin/myosin contraction



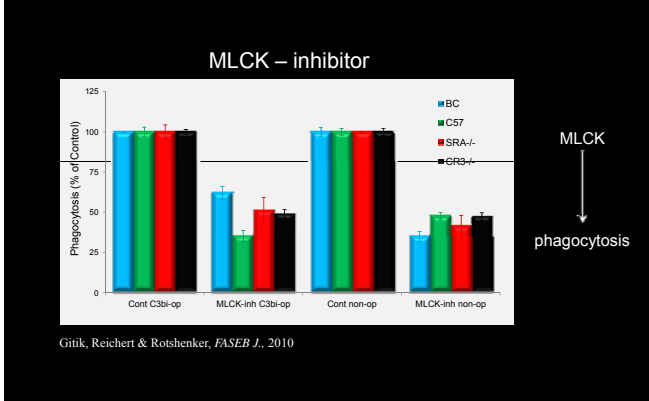
MLCK-dependent phagocytosis of myelin



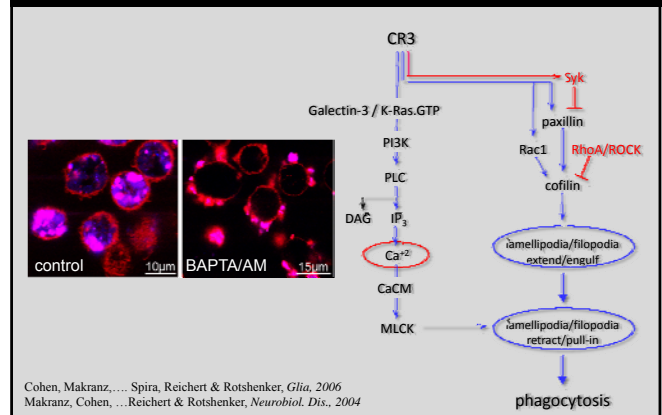
MLCK activates myelin phagocytosis by phosphorylating MLC (p-MLC)



MLCK activates myelin phagocytosis



The signaling network of myelin phagocytosis



CR3-mediated myelin phagocytosis: engulfment and internalization

